Accepted Manuscript

Alternative tandem cyclisation pathways in the reaction between imines and enones

P. Ricardo Girling, Andrei S. Batsanov, Adam D.J. Calow, Hong C. Shen, Andrew Whiting

PII: S0040-4020(16)30006-0

DOI: 10.1016/j.tet.2016.01.006

Reference: TET 27413

To appear in: *Tetrahedron*

Received Date: 19 November 2015

Revised Date: 24 December 2015

Accepted Date: 5 January 2016

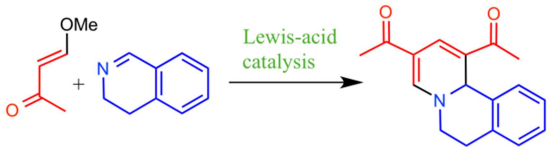
Please cite this article as: Girling PR, Batsanov AS, Calow ADJ, Shen HC, Whiting A, Alternative tandem cyclisation pathways in the reaction between imines and enones, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.01.006.

Alternative tandem cyclisation pathways in the reaction between imines and enones

Leave this area blank for abstract info.

P. Ricardo Girling,[a] Andrei S. Batsanov,[a] Adam D. J. Calow,[a] Hong C. Shen,[b] Andrew Whiting[a*]

[a]*Centre for Sustainable Chemical Processes, Dept. of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK.* [b]*Merck & Co., RY800-C114, 126 East Lincoln Avenue, PO Box 2000, Rahway, NJ 07065-0900, USA.*



Tetrahedron
journal homepage: www.elsevier.com

Alternative tandem cyclisation pathways in the reaction between imines and enones

P. Ricardo Girling,[a] Andrei S. Batsanov,[a] Adam D. J. Calow,[a] Hong C. Shen,[b] Andrew Whiting[a]*

[a]*Centre for Sustainable Chemical Processes, Dept. of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK.*
[b]*Merck & Co., RY800-C114, 126 East Lincoln Avenue, PO Box 2000, Rahway, NJ 07065-0900, USA.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

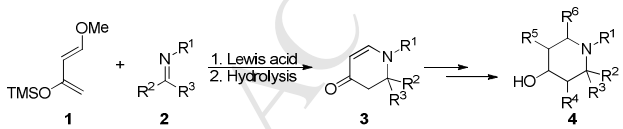
Keywords:
Aza-Diels-Alder
Lewis-acid
Homogeneous catalysis
Cycloaddition
Dihydropyridine
Piperidenone

ABSTRACT

Dihydroisoquinoline reacts with Danishefsky's diene under Lewis acidic conditions or neat, to give low to moderate yields of the formal aza-Diels-Alder, [4+2]-cycloadduct. However, using methoxyvinyl methylketone with Lewis acid catalysis does not give the aza-Diels-Alder adduct, rather a formal [2+2+2]-cycloaddition occurs to provide access to a diacetyl dihydropyridine. Increased Lewis acid loading results in reduced dihydropyridine formation, and instead, a trimerisation reaction of the methoxyvinyl methyl ketone, to give 1,3,5-triacetylbenzene from a different formal [2+2+2]-cycloaddition. The formal [4+2]-cycloaddition reaction of methoxyvinyl methylketone requires a cyclic imine in order to form the dihydropyridine because the reaction with acyclic imines produced a dihydropyridine from a formal [1+2+1+2]-cycloaddition. Evidence resulting from the isolation of reaction intermediates and *in situ* spectroscopic studies, shows that the reaction between *3*,4-dihydroisoquinoline and methyl vinyl ketone, catalysed by oxy-philic Lewis acids, proceeds *via* a Mannich-Michael pathway and an imminium ion species. All reactions occur by one-pot cascade routes.

1. Introduction

Natural products containing the piperidine ring system[1] are well known to be biologically active[2] and many analogues have been developed for their potential medicinal properties.[3] The synthesis of these types of six-membered nitrogen heterocycles can be achieved *via* a Lewis acid-catalysed, formal aza-Diels–Alder reaction involving an imino dienophile and a conjugated diene[4] as outlined in Scheme 1 (*e.g.* using electron rich siloxy dienes such as Danishefsky's diene 1).[5]

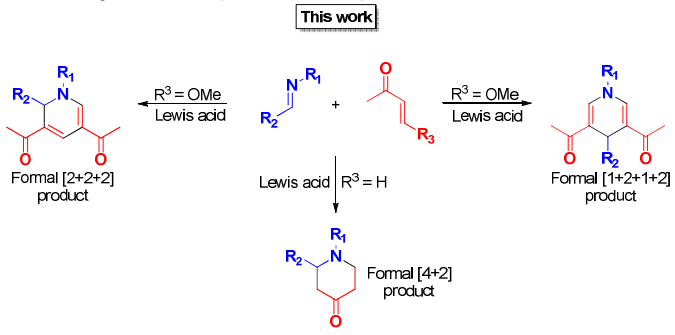


Scheme 1: A general approach to poly-substituted piperidines.

The mechanism involved is potentially a concerted [4+2]-cycloaddition, however, in most cases it actually proceeds through a step-wise Mannich-Michael reaction.[6] Nevertheless, the formal Diels-Alder process is a powerful synthetic strategy for accessing piperidinones **3**, from which more complex piperidines **4** can be accessed.[7]

As part of our ongoing development of novel approaches to piperidinones and their derivatives, typically employing Lewis acid catalysis[8] and associated mechanistic observations,[9] we have been examining the reactions of acyclic electron deficient imines with various dienes. In addition, we recognised the potential of this approach for the synthesis of polycyclic nitrogen-containing heterocycles of general type **6**, starting from cyclic imines. Heterocycles of this type occur naturally in representative structures with varied biological activity[10] and, hence, are worthy of further study in order to access formal aza-Diels-Alder adducts for elaboration to more substituted targets.

In this paper, we report the synthesis of *N*-heterocyclic compounds from imines and enones *via* different tandem cyclisation pathways. The different modes of reaction that we investigated include formal [2+2+2], [1+2+1+2] and [4+2] cascade cyclisations (see Scheme 2).

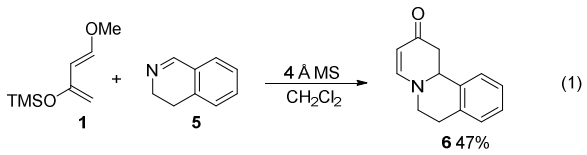


Scheme 2: The synthesis of *N*-heterocyclic compounds from imines and enones *via* different tandem cyclisation pathways

2. Results and discussion

2.1 Synthesis of piperidenone and dihydropyridine analogues

Our starting point for the synthesis of piperidinones of type **3** was to examine the racemic formation of tricyclic piperidinone **6** as a prelude to developing a catalytic asymmetric route. Hence, we examined the reaction of Danishefsky's diene **1** under Lewis acid-catalysed conditions with readily accessible[11] imine **5** (Eqn. 1).



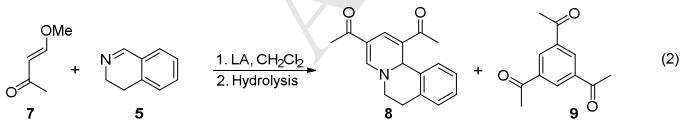
(1)

Danishefsky's diene reacted on its own with the imine, most likely initiated *via* nucleophilic attack of the diene on the imine, followed by cyclisation, *i.e.* through a Mannich-Michael mechanism.[6] After hydrolysis and purification, piperidinone **6** could be isolated in up to 47% yield. However, none of these reactions were completely clean according to TLC analysis, and therefore, an improved methodology to systems of type **3** was still required.

It was considered that direct reaction of 4-methoxy-3-buten-2-one **7** with imine **5** in the presence of a suitable catalyst might induce formation of an enolate equivalent *in situ*. This might be expected to cyclise to give the desired cycloadduct, hence, avoiding the use of Danishefsky's diene. This approach would be a step-wise addition, cyclisation, elimination, which nonetheless would accomplish the desired formal cycloaddition. Thus, exposure of 4-methoxy-3-buten-2-one **7** under a range of Lewis acid and secondary amine-catalysed reaction conditions was examined as in Eqn. 2, resulting in complex mixtures of products. However, the use of ytterbium(III) triflate as Lewis acid catalyst did not provide piperidenone **6**. Instead, the diacetyl-dihydropyridine **8** was obtained in 20% yield; its structure was later proved by X-ray crystallography (see SI). The identification of product **8**, derived from a formal [2+2+2]-cycloaddition, through a cascade process, prompted us to examine this reaction in more detail.

2.2 Formal [2+2+2]-cycloaddition

The unexpected observation of the formation of the [2+2+2]-cycloaddition product **8** is almost unprecedented,[10] and therefore, further investigations into this reaction started by varying the catalyst and its loading. It was found that scandium(III) triflate was particularly effective for these reactions (see Eqn. 2 and Table 1), however, a side-product **9** was observed, especially at higher catalyst loadings.



(2)

The high symmetry of the impurity meant that it was readily identified[12] as 1,3,5-triacetylbenzene **9** (the structure was also confirmed by X-ray crystallographic studies, see SI); a structure which has been recently reported to readily assemble by heating 4-methoxy-3-buten-2-one **7** in water at 150 °C.[13] The results in Table 2 also show that the formation of trimer **9** was favoured over the formation of dihydropyridine **8** with increasing Lewis acid catalyst loading. Without the addition of Lewis acid, no reaction occurred (Table 1, Entry 1). With low Lewis acid catalyst loading (5%), low conversion to adduct **8** was observed (Table 1, entry 2). Optimal formation of dihydropyridine **8** occurred at 10 mol% catalyst loading, with no trimer **9** being produced (Table 1, entry 3). With 20 mol% catalyst loading, trimer **9** started to appear (Table 1, Entry 4), though to obtain complete conversion to the trimer alone, stoichiometric Lewis acid seemed to be required (Table 1, Entry 5).

Table 1: Effect of catalyst loading on the reaction of **5** with **7** (Eqn. 2).

Entry	Lewis acid (mol%)	Yield **8** (%)[a]	Yield **9** (%)[b]
1	0	0	-
2	5	<10[b]	-
3	10	61	-
4	20	48	<5
5	100	0	>55

[a]Isolated yield after silica gel chromatography. [b]Conversion estimated from the crude ^{1}H NMR spectrum.

As can be observed from Table 2, relatively low to moderate yields of the formal [2+2+2]-cycloadduct **8** were obtained, *i.e.* in the 20-40% range, though in a convenient manner and a pure form, through direct trituration of the crude reaction product. Despite the low yields obtained (Table 2), these studies provided some additional useful information about the catalytic process. The use of either $Sc(OTf)_3$, $Yb(OTf)_3$, or its hydrate as catalysts made little difference to the isolated yields (Table 2, entries 1, 3 and 5), with or without molecular sieves (Table 2, entries 3 and 4). Different solvents also had no significant effect, except when using methanol or acetonitrile, in which cases, the yields tended to be lower (Table 2, compare entries 9, 12-16 with entries 10 and 11).

Having examined the origin of the unwanted by-product **9** in order to prevent its formation, optimisation of the synthesis of dihydropyridine **8** was explored, *i.e.* the effect of catalyst, catalyst loading, enone equivalents, solvent, additives and work up procedure, as outlined in Table 2. Further reaction optimisation (Eqn. 2) was carried out by examining a wider-range of Lewis acids in order to see if conversion could be improved (Table 3).

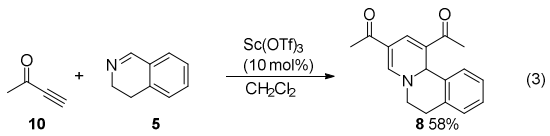
The results, shown in Table 3, demonstrate that the Lewis acids that afforded the highest yields were $Fe(OTf)_3$ and $Ga(OTf)_3$ (Table 3, entries 7 and 8), whilst the chiral Lewis acid $Eu(hfc)_3$ was inactive, even at higher temperatures (Table 3, entries 4 and 5). In addition, higher yields of **8** were obtained when the reaction mixture was purified by silica gel chromatography (*e.g.* Table 4, entries 1-3). This was further optimised to ensure good solubility of **8** (Table 3, entries 6-10) to enable efficient elution of the product off the column during purification. Overall, the highest yields of **8** obtained were 88% for entries 7 and 8 (Table 4), which, considering the low yields obtained initially and the complexity of the reaction mixtures, was very satisfactory. In fact, this yield equates to each of the three new bonds being formed with 96% efficiency during the formation of formal [2+2+2]-cycloadduct **8**.

Table 2: Optimisation studies of the [2+2+2]-cycloaddition reaction to give **8**, as in Eqn. 2.

Entry	Enone equiv. **7**	Catalyst (mol%)	Solvent	Time (days)	Additive	Yield **8** (%)[a]	Yield **9** (%)[b]
1	5	$Yb(OTf_3)$ (20)	CH_2Cl_2	2	-	40	<5
2	2	$Yb(OTf_3)$ (20)	$CDCl_3$	1	-	30	<5
3	2	$Sc(OTf)_3$ (10)	$CHCl_3$	2	-	41	0
4	2	$Sc(OTf)_3$ (10)	$CHCl_3$	2	4 Å MS	42	0
5	2	$Yb(OTf_3)$ hydrate (10)	$CHCl_3$	2	-	40	0
6	3	$Sc(OTf)_3$ (10)	$CHCl_3$	1-2	-	40	0
7	4	$Sc(OTf)_3$ (10)	$CHCl_3$	2	-	50	0
8	5	$Sc(OTf)_3$ (10)	$CHCl_3$	2	-	20	0
9	4	$Sc(OTf)_3$ (10)	EtOAc	3	-	20	0
10	4	$Sc(OTf)_3$ (10)	MeOH	3	-	15	0
11	4	$Sc(OTf)_3$ (10)	CH_3CN	3	-	15	0
12	4	$Sc(OTf)_3$ (10)	THF	3	-	30	0
13	4	$Sc(OTf)_3$ (10)	Et_2O	3	-	21	0
14	4	$Sc(OTf)_3$ (10)	hexane	3	-	19	0
15	4	$Sc(OTf)_3$ (10)	CH_2Cl_2	3	-	21	0
16	4	$Sc(OTf)_3$ (10)	toluene	3	-	20	0
17	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	H_2O	15	0
18	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	4 Å MS	25	0
19	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	-	20	0

[a]Isolated yield after work up by trituration. [b]Conversion estimated from the crude ^{1}H NMR spectrum.

Interestingly, this cycloadduct **8** was also isolated in 58% yield when using butyne-one **10** (Eqn. 3) under scandium(III)-catalysed conditions, demonstrating that this yne-one might be involved in the reaction mechanism.



(3)

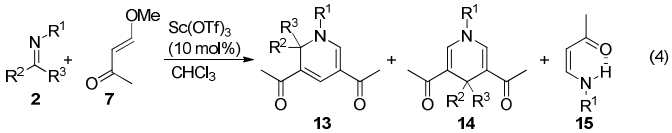
Table 3: Effect of different Lewis acids upon the formal [2+2+2]-cycloaddition reaction to give **8**, as in Eqn. 2.

Entry	Lewis acid (10 mol%)[a]	Yield of **8** (%)[b]
1	$Yb(OTf)_3$	61[c]
2	$Sc(OTf)_3$	46[c]
3	$In(OTf)_3$	49[c]
4	$Eu(hfc)_3$	-
5	$Eu(hfc)_3$ (60 ºC)	-
6	$Sc(OTf)_3$ (+ pybox 10 mol%)	82[d]
7	$Fe(OTf)_3$	88[d]
8	$Ga(OTf)_3$	88[d]
9	$Yb(OTf)_3$	87[d]
10	$In(OTf)_3$	81[d]

[a]All reactions carried out in CH_2Cl_2. [b]Isolated yield after purification by silica gel chromatography. [c]Purification eluent EtOAc. [d]Purification eluent EtOAc:CH_2Cl_2 (4:1).

2.3 Reaction scope and alternative reaction pathways: a formal [1+2+1+2] pathway to dihydropyridines.

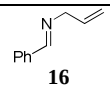
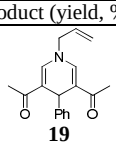
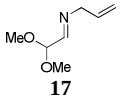
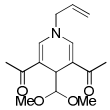
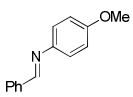
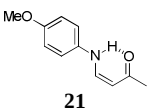
In order to further understand the formal [2+2+2]-cycloaddition reaction that provided **8**, the use of acyclic imines was examined. Different acyclic imines **2** were reacted in the presence of 10 mol% scandium(III) triflate in the expectation of forming the diacetyl products **13**. However, after purification by silica gel chromatography, dihydropyridine isomers **14** were instead obtained (Eqn. 4 and Table 4),[14] together with an acyclic precursor **15**.



(4)

Dihydropyridines **19** and **20** (Table 4, entries 1, 2) were unexpected products, being formed by a formal [1+2+1+2]-cycloaddition and in a four-component reaction.[14] Under these reaction conditions, the starting imine must have hydrolysed, freeing the amine and aldehyde to undergo the multi-component reaction;[15] related reactions have been reported by us.[8,9] Further evidence for the probable mechanism of this multi-component assembly comes from the isolation of the Michael adduct **21**,[16] which results from the reaction between the free amine and enone **7** (Table 4, entry 3). Acyclic imines appear to be substantially more prone to hydrolysis to the amine and aldehyde, and can then undergo the formal [1+2+1+2]-cycloaddition mode. This suggests that the system needs to be completely anhydrous for the [2+2+2]-cycloaddition to occur. However, when the reaction was performed under rigorously dry conditions, the major reaction products were still those derived from the formal [1+2+1+2]-cycloaddition, rather than the [2+2+2]-product, showing that even under these dryer conditions, the imine was still hydrolysed, though we cannot rule out a related role for methanol in this reaction.

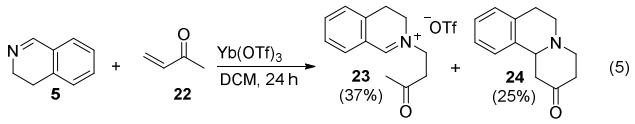
Table 4: Reactions between acyclic imines **2** and enone **7**, as in Eqn. 4.

Entry	Imine	Enone equiv.	Product (yield, %)[a]
1	 **16**	4	 **19**
2	 **17**	4	 **20**
3	 **18**	2.5	 **21**

[a]Isolated yield after purification by silica gel chromatography.

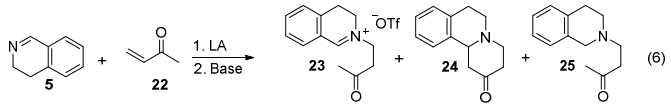
2.4 Developing the formal [4+2]-cycloaddition reaction

Having explored the formal [2+2+2]-cycloaddition, which was possible due to the presence of a β-leaving group (*e.g.* **7**), attention was turned to enones without a leaving group in the β-position to see if the formal [4+2]-cycloadduct could be accessed, *i.e.* formerly through a conjugated enol-ene system. To this end, methyl vinyl ketone **22** (2 equiv.) was reacted with imine **5** in the presence of $Yb(OTF)_3$ (20 mol%), as shown in Eqn. 5.



(5)

This reaction proceeded to give a mixture of products, however, the major products consisted of **23** (37%) and the formal aza-Diels-Alder [4+2]-cycloadduct **24** (25%). It is important to note that derivatives of type **24** are of considerable pharmacological interest due to their biological activity.[19]



(6)

Table 5: Optimising the reaction between imine **5** and enone **22** to give the formal *aza*-Diels-Alder adduct **24**, as shown in Eqn. 6.

Entry	Lewis acid (%)	Base	Solvent	**23** (%)	**24** (%)	**25** (%)
1	$In(OTf)_3$ (20)	NaOH	CH_2Cl_2	-	62	-
2[d]	$In(OTf)_3$ (20)	STAB[c]	CH_2Cl_2	-	12	-
3[e]	$In(OTf)_3$ (20)	NaOAc	CH_2Cl_2	-	11	-
4	$In(OTf)_3$ (20)	NaOAc	CH_2Cl_2	-	45	-
5	$In(OTf)_3$ (40)	NaOAc	CH_2Cl_2	-	59	-
6	$In(OTf)_3$ (40)	NaOH	EtOAc	-	37	-
7	$In(OTf)_3$ (40)	NaOH	MeOH	-	37	-
8	$In(OTf)_3$ (40)	NaOH	MeCN	-	27	-
9	$In(OTf)_3$ (40)	NaOH	THF	-	5	-
10[d]	$In(OTf)_3$ (40)	STAB[c]	CH_2Cl_2	-	11	34
11	$Sc(OTf)_3$ (10)[a]	NaOH	CH_2Cl_2	-	39[b]	-
12	$Fe(OTf)_2$ (20)	NaOH	CH_2Cl_2	-	35	-
13	$Ga(Otf)_3$ (20)	NaOH	CH_2Cl_2	-	18	-

All reactions were stirred for 24 hours at rt. [a]Reaction was conducted in the presence of chiral PyBOX (10%). [b]Enantiomeric excess was found to be 0% by chiral HPLC (see SI). [c]$NaBH(OAc)_3$. [d]Reaction was quenched with NaOH. [e]Reaction was quenched with brine.

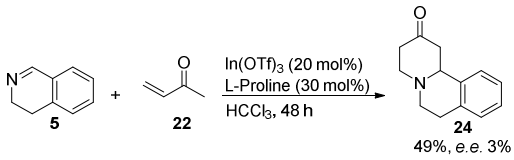
The reaction shown in Eqn. 5 is significant in that as well as providing easy access to biologically interesting compounds, it also provides intermediates which may give mechanistic insights into this reaction (*vide infra*). Indeed, Eqn. 5 also demonstrates the potential for an efficient formal [4+2]-cycloaddition reaction between **5** and **22**, giving access to the desired product **24**. The presence of **23** can be rationalised by a Michael-type reaction, whereby the nucleophilic imine **5** adds to the electropositive β-carbon of **22**. The simple interpretation of this result is that **23** is an ideal precursor for an intramolecular 6-*endo-trig* Mannich-type cyclisation reaction to derive **24**. The question is then whether this is indeed the case, or whether the reaction is more complex than it appears. To this end, we next investigated the formal [4+2]-cycloaddition reaction of **5** and **22** by screening a series of oxy-philic Lewis acid and base combinations (Eqn. 6), with the aim of optimising the formation of the cyclic adduct **24**. The results are shown in Table 5.

$In(OTf)_3$ (20 mol%), in combination with the addition of NaOH, gave the formal aza-Diels-Alder adduct **24** in 62% yield (Table 5, entry 1). Further investigations varying the Lewis acid loading, base additive and solvent (Table 5, entries 1-9) did not improve the reaction to any significant extent. Even with increased catalyst loading, formation of **24** could not be increased past 62%. With this in mind, we turned our attention to alternative Lewis acids. It was found, however, that the most efficient catalyst for forming the adduct **24** was still $In(OTf)_3$. Interestingly, when $Sc(OTf)_3$ was employed as the catalyst (Table 5, entry 11) and PyBox (10%) was used as an additive, with the aim of developing the asymmetric formal [4+2]-cycloaddition, the cyclic adduct **24** was obtained in 39% yield, however, with no asymmetric induction.

2.5 Alternative approaches to asymmetric induction in the formal [4+2]-cycloaddition reaction

With the results from Table 5 in hand, attention was turned to trying to solve the issue of obtaining asymmetric induction in the reaction outlined in Eqn. 6, and particularly, through the enantiocontrolled cyclisation of iminium species **23**, either from *in situ* generation or after isolation. Advances in asymmetric catalysis and especially organocatalysis[20] provided a number of possible options worthy of exploration in order to develop the required asymmetric cyclisation methodology.

Initially we investigated chiral secondary amines as potential catalysts for forming **24** in an enantioselective manner.[20a] L-Proline (20 mol%) was employed in parallel with $In(OTf)_3$ (20 mol%) to afford the adduct **24** in 49% yield (see Eqn. 7). An *e.e.* of 3% was observed by chiral HPLC. However, this level of asymmetric induction can be considered to be within experimental error, despite clean product formation and HPLC chromatogram.



(7)

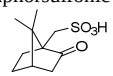
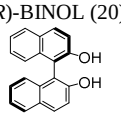
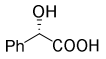
In addition to these results, it should be noted that Jørgensen *et al.* developed an efficient asymmetric organocatalytic protocol, which is analogous to this work and involves an iminium ion-aldehyde cyclisation.[23] Although L-proline provided cyclisation, there was no asymmetric induction, and indeed, a C2-symmetric chiral pyrrolidine was required in order to effect asymmetric induction.

Early studies on the synthesis of **24** demonstrated that this could be achieved by reacting methyl vinyl ketone **22** and imine **5** in the presence of HCl (reaction heated to reflux), to give the cyclic product **24**.[1917] In addition, chiral Brønsted acids have, in recent years, proven to be efficient catalysts for a series of asymmetric transformations, including Diels-Alder reactions.[24] We therefore wondered whether, through the addition of chiral

Brønsted acids, the formal [4+2]-cycloaddition reaction between **5** and **22** could be achieved. In this context, chiral Brønsted acid catalysis was examined by using the chiral phosphoric acid (*S*)-**26**[24] in the formal [4+2] cycloaddition (see Table 6, entry 11). Acid (*S*)-**26** catalysed the transformation, giving the cyclic adduct **19** in 44% isolated yield; however, chiral HPLC analysis revealed that the product was racemic.

In addition to (*S*)-**26**, several other chiral and achiral Brønsted acids were examined under these conditions (see Table 6) to see what types of systems could affect the formal cycloaddition reaction between **5** and **22**.

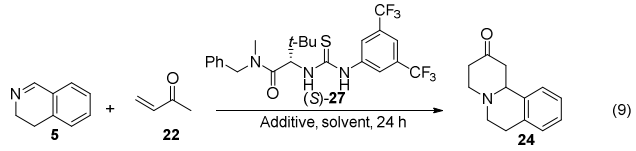
Table 6. Brønsted acid catalysed cyclisation between **5** and **22**, to **24**, as shown in Eqn. 8.

Entry	Catalyst (%)	Conv. **24** (%)[a]
1	-	0
2	(*R*)-Camphorsulfonic acid (20) 	57
3	(*R*)-Camphorsulfonic acid (40)	60
4	Benzoic acid (20)	79
5	TsOH (20)	50
6	(*R*)-BINOL (20) 	0
7	*p*-Nitrobenzoic acid (20)	64
8	Chloroacetic acid (20)	86 [83][b]
9	4-Phenylbutyric acid (20)	57
10	(*S*)-Mandelic acid (20) 	70
11[c]	Chiral phosphporic acid (20)	[44][b]

[a]Determined by ^{1}H NMR spectroscopic analysis. [b]Isolated yield. [c]THF used as solvent. The reaction was heated to reflux for 16 h.

No asymmetric induction was achieved in any cases. It should be noted that a relationship between pK_a and conversion was observed, whereby the most efficient acid catalyst was found to be the achiral chloroacetic acid, leading to the formation of (*rac*)-**24** in 83% isolated yield.

Next, we examined the potential of thiourea catalysts [*e.g.* (*S*)-**27**] to catalyse the formal [4+2]-cycloaddition reaction. It was anticipated that the thiourea (*S*)-**27** would hydrogen-bond to the carbonyl of methyl vinyl ketone **22**, thus further activating the C_β to nucleophilic attack. Indeed, subsequent Michael-addition (of **5**) would, presumably, yield the analogous *O*-hydrogen bonded enolate; after suitable isomerisation to the external enolate. The resulting enolate would then be ideally placed for the required asymmetric 6-*endo-trig* cyclisation. The results of these studies are shown in Eqn. 9 and Table 7.



The room-temperature reaction between **5** and **22**, in the presence of (*S*)-**27**, failed to give the desired product **24** (Table 7, entry 1). The addition of catalytic amounts (3 mol%) of chloroacetic acid (Table 7, entry 2), in parallel with (*S*)-**27**, afforded the cyclic adduct (*rac*)-**24** in 60% conversion (by ^{1}H NMR analysis). Heating the reaction to 60 °C for 24 h had no influence and, indeed, the formation of **24** was not achieved.

Table 7. Thiourea-catalysed reaction between imine **5** and enone **22** to give the formal *aza*-Diels-Alder adduct **24**, as shown in Eqn. 8

Entry	Temp. °C	(*S*)-**27** (%)	Additive (%)	Solvent	Conv. **24** (%)[a]
1	r.t.	20	-	CH_2Cl_2	0
2	r.t.	10	Chloroacetic acid (3)	CH_2Cl_2	60
3	60	10	-	Toluene	0

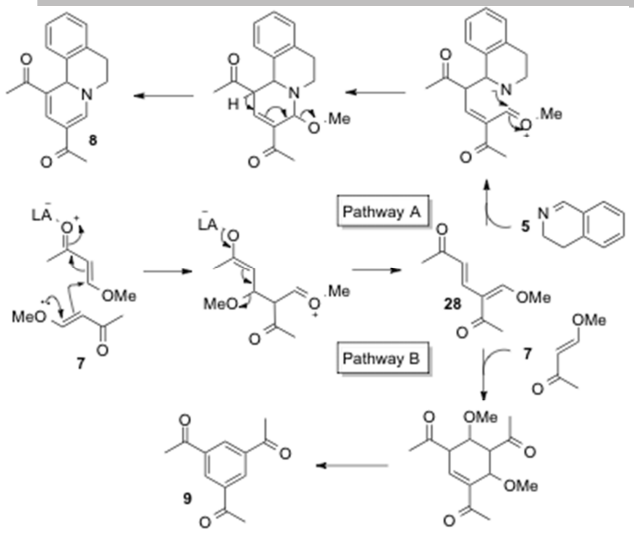
[a]Measured by ^{1}H NMR analysis. Product **24** was found to be racemic by chiral HPLC analysis.

The asymmetric formal [4+2]-cycloaddition reaction between **5** and **22** was proving to be elusive. Regardless, the formation of **24** by general Lewis acid catalysis or, indeed, Brønsted acid catalysis, did efficiently produce access to formal cycloadduct **24** with varying degrees of efficiency. In order to try and find a solution to the asymmetric induction issue, the development of a more detailed mechanistic understanding of the reaction was necessary. Along this line, a study into the mechanism of the formal [4+2]-cycloaddition was undertaken through *in situ* spectroscopic techniques (this will be discussed below).

2.6 Understanding the mechanism of the formal [2+2+2], [1+2+1+2] and [4+2]-cycloaddition reactions.

2.6.1 Proposed mechanism for the formal [2+2+2]-cycloaddition

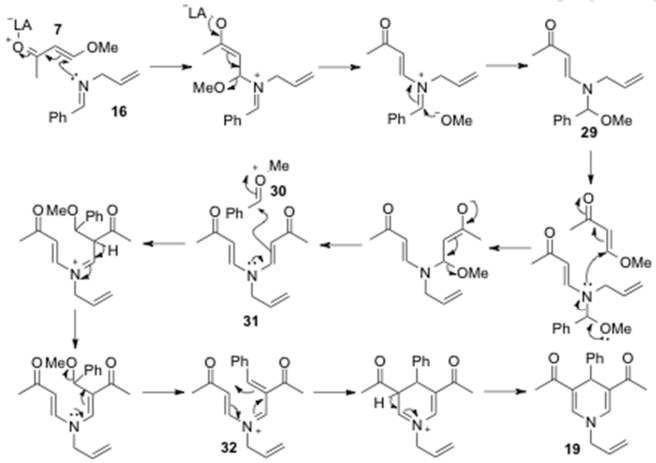
It is interesting to speculate upon the mode of activation of enone **7** by the Lewis acid which triggered trimerisation. This might occur as outlined in Scheme 3, *i.e.* through dimerisation, followed by elimination to give electron deficient diene-dione **28**, which can then derive cycloadduct **8** (Pathway A) through a Lewis-acid catalysed Diels-Alder reaction. Alternatively, triacetylbenzene **9** can be explained from the common intermediate **28** undergoing a third reaction with **7**, which leads to the trimer **9** (Pathway A).



Scheme 3: Proposed mechanism for the formation of the dihydropyridine **8** or the trimer **9**.

2.6.2 Proposed mechanism for the formal [1+2+1+2]-cycloaddition

It is possible to speculate that the formal [1+2+1+2]-cycloaddition reaction can be rationalised by assuming initial Michael-addition of imine **16** to the activated enone **7**. Methoxide elimination and hemi-aminal formation would result in species **29**. Addition of a further enone **7** to **29**, elimination of methoxide and trapping the activated benzaldehyde equivalent **30** *via* diene-amine **31**, would lead to imminium-diene **32**, following further methoxide elimination. A [3,3]-sigmatropic shift cyclisation of **32**, followed by iminium-enamine conversion, would provide the formal [1+2+1+2]-cycloaddition product **19**.



Scheme 4: Rationalisation of the observed formal [1+2+1+2]-cycloaddition reaction.

2.6.3 Proposed mechanism for the formal [4+2]-cycloaddition

We have recently studied the direct *versus* conjugate addition reaction of primary amines to enones and enals using *in situ* IR spectroscopy (ReactIR™).[25] *In situ* IR spectroscopy was particularly useful here because it allowed the real-time monitoring of the reactions, providing instant feedback with regards to reaction progression, and was especially useful when reactions were conducted under air- and moisture-sensitive conditions.[26] It was, therefore, ideal for the investigation of the formal [4+2]-cycloaddition reaction as outlined in Eqn. 9, in order to gain mechanistic insight into this reaction. Hence, the investigation was started using *in situ* IR spectroscopy and by adding three equal portions of $In(OTf)_3$ (→35 mol%, *i.e.* stoichiometric overall, with respect to triflate) to a stirred CH_2Cl_2 solution of imine **5** and methyl vinyl ketone **22** (1.1 equiv.), and following the reaction over time. The results are shown in Figure 1. Figures 1 and 2 clearly show that upon the addition of the oxy-philic $In(OTf)_3$, Lewis acid activation of methyl vinyl ketone **22** occurs, though coordination to the carbonyl. This results in a rapid Michael-addition by the nitrogen of imine **5**, as judged by the loss of the C=N stretch (of **5**) at 1630 cm^{-1} in parallel with the C=O of **22** at 1682 cm^{-1}. This is matched with the tandem appearance of a new C=O stretch at 1722 cm^{-1}, which is additionally supported by characterisation data of the pure iminium compound **23** (see Figure 2).

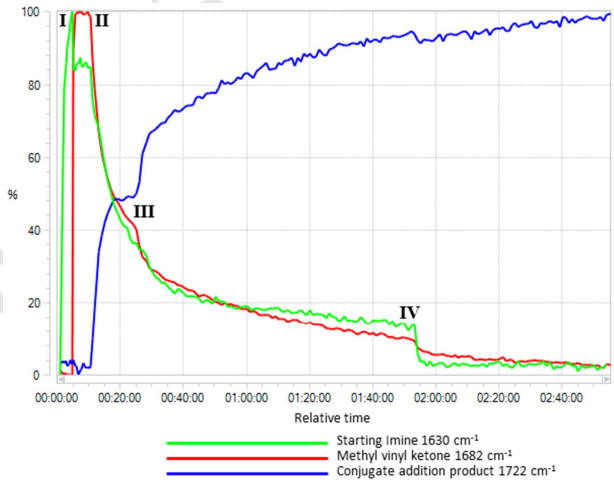


Figure 1: ReactIR – Reaction progression: **I** addition of imine **5** and methyl vinyl ketone **22**; **II** → **IV** addition of 3 equal portions of $In(OTf)_3$, which shows the loss of **5** and **22** and the rise of the conjugate addition product **23**.

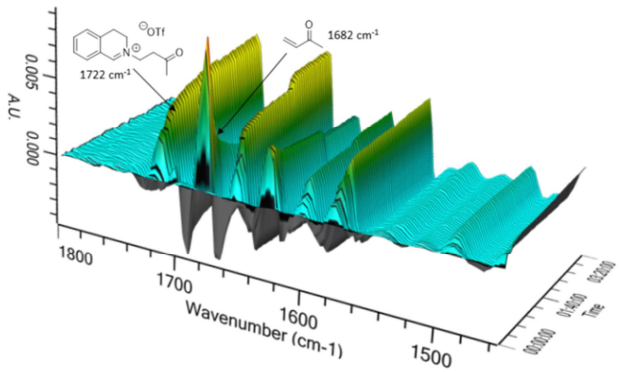
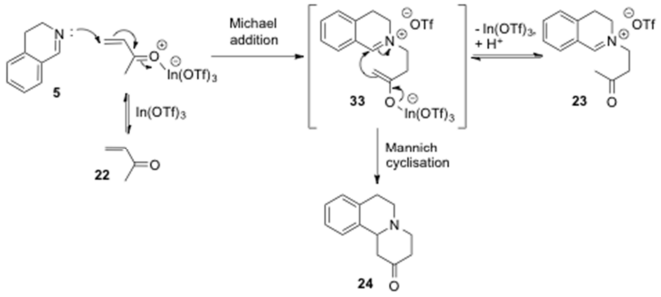


Figure 2: ReactIR graphical output – shift of C=O stretch at 1682 cm^{-1} to C=O stretch at 1722 cm^{-1} is consistent with conjugate addition of imine **5** to enone **22**.

The real-time reaction monitoring suggests that the presumed Michael-Mannich pathway predominates in the formal [4+2] cycloaddition (see Scheme 5), and presumably proceeds

through an indium-catalysed mechanism and enolate species **33.** Moreover, the formation of **23** appears to be facile and, indeed, the formation of **24**, *via* the Mannich-step (Scheme 5), appears to be slow and could well be rate-determining (as shown by *in situ* IR spectroscopic analysis).

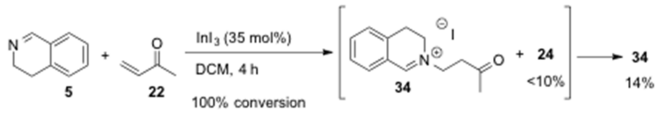


Scheme 5: Proposed mechanism for the formation of the dihydropyridinone **24**.

The *in situ* IR study was also compared with ^{1}H NMR analysis, and in particularly the Mannich-step of the reaction (see SI for NMR spectra) using preformed iminium triflate **23** (formed under the same reaction conditions as in the *in situ* IR spectroscopic study, except that the solvent was switched to $CDCl_3$ to allow ^{1}H NMR monitoring). Once **23** had formed (ratio of **23**:**24** was 1.0:0.7, respectively), several drops of NaOD (in D_2O) were added to the NMR tube and the sample vigorously shaken. The resulting ^{1}H NMR spectrum (acquired within 15 minute), showed, to our surprise, the instantaneous loss of the iminium ion **23**, but this was not mirrored by the formation of the cycloadduct **24**. Instead, the reaction proceeded to give a mixture of imine **5**, enone **22** and cycloadduct **24**. The regeneration of the starting imine **5** presumably occurs through a facile β-elimination.

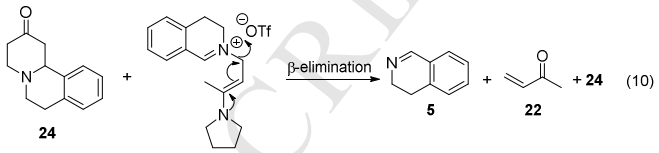
The lack of success in the attempted asymmetric cyclisation of the iminium ion **23** led us to examine the potential reactivity of the analogous iodide towards **23**, *i.e.* where the triflate was exchanged for iodide using InI_3 instead of $In(OTf)_3$ (*vide supra*). Initially, the iminium iodide was generated *in situ* by reaction of enone **22** with imine **5** (evidence of iminium ion formation from ^{1}H NMR analysis). Subsequent attempts at direct cyclisation were consistent with those of the analogous triflate **23**.

The lack of a successful asymmetric entry to cycloadduct **24** through the *in situ* formation of **23** led us to check that iminium ion **23** was indeed being formed. Compounds of type **23** are rather unusual. For example, **23**, despite being an iminium ion salt, was obtained after column chromatography. This may cast doubt on its structural assignment, however, all characterisation data suggests this to be the case, as opposed to the corresponding triflate adduct, *i.e.* α-amino triflate. By comparison with the few reports found in the literature,[27] the fact that the iminium ion CH was observed at low field in the ^{1}H NMR spectrum (δ 9.12 for **23**), compared to δ 7.95 for an α-amido triflate seems to agree with our structural assignment being the corresponding iminium ion. Hence, in order to further corroborate these observations, we prepared the iodide **34** (see Scheme 6), with the hope of producing the crystalline material (suitable for crystallographic studies) to confirm, beyond doubt, the structure of **23** (through comparison with **34**). However, the analogous iodide **34** was obtained, after chromatography, as an oil. Regardless, the iodide **34** had consistent characterisation data with that of the triflate **23** (similar structures exist in the literature[24]) with the corresponding iminium CH being observed at a similar low field ^{1}H NMR chemical shift of δ 9.81.



Scheme 6: Formation of iodide **34** *in situ*; isolated after column chromatography in 14% yield.

The facile β-elimination of imine **5** from either adducts **23** or **34** was also found to occur under other conditions. For example, when adduct **23** was formed *in situ*, addition of pyrrolidine was found to catalyse β-elimination, leading to the formation of imine **5** (see SI and Eqn. 10).



This can be rationalised by initial iminium ion formation, through condensation, with subsequent tautomerisation to the internal enamine, leading to facile elimination. The same generic outcome was found when using the respective Jørgensen and Hayashi catalysts,[22] which, in addition to the observed conjugate addition of amines to methyl vinyl ketone **22**,[25] explains the lack of *e.e.* and poor catalytic performance (see above).

3. Conclusions

In summary, a new class of reaction has been found when reacting a conformationally locked cyclic imine **5** with 4-methoxy-3-buten-2-one **7**, in order to access diacetyl dihydropyridine **8** in the presence of a Lewis acid. This is thought to go through a formal [2+2+2]-cycloaddition reaction pathway. Using higher Lewis acid loadings, however, trimer **9** predominantly forms. The use of acyclic imines failed to provide these types of formal [2+2+2]-cycloadducts, rather formal [1+2+1+2]-cycloaddition products were obtained. Using Danishefsky's diene **1** instead of the unactivated enone **7** afforded the aza-Diels-Alder adduct **6**, *i.e.* through a formal [4+2]-cycloaddition that was most likely a Mannich-Michael process. In addition, the Lewis acid catalysed Michael-Mannich reaction was examined, leading to the development of a formal [4+2]-cycloaddition pathway towards the synthesis of the aza-Diels-Alder adduct **24**. *In situ* spectroscopic investigations were conducted, which shed light on this process and, indeed, support the Michael-Mannich pathway. Further applications of these one-pot assembly processes to derive novel heterocycles are under examination.

4. Experimental section

3,4-Dihydroisoquinoline (5)

Prepared following standard literature procedure[11]: ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.3 (br s, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 3.73 (t, *J* = 7.8 Hz, 2H), 2.71 (t, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 136.4, 131.1, 128.5, 127.4, 127.2, 127.1, 47.4, 25.0; IR νmax (neat) 1626 cm^{-1}; LRMS (TOF ES+), 132.2 (100%) $[M+H]^+$; HRMS (TOF ES+),

calculated for $C_9H_9N+H^+$, 132.08078; found 132.08092. All spectroscopic and analytical properties were found to be identical to those reported in the literature.[11]

*6,7-Dihydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**6**)*

To **5** (0.131 g, 1.0 mmol) and 3 Å molecular sieves (1 g) under argon was added Danishefsky's diene **1** (0.240 mL, 1.2 mmol) dropwise. The reaction mixture was stirred at rt for 48 h, diluted with CH2Cl2 (2 5 mL), filtered and concentrated *in vacuo*. Purification by silica gel chromatography (3:1, EtOAc:hexane, to 100%, EtOAc, as eluent) afforded **6** as a pale orange solid (0.093 g, 47%): R_f. 0.05 (2:1, EtOAc:hexane as eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.17 (m, 4H), 7.16 (dd, *J* = 7.4, 0.8 Hz), 5.08 (dd, *J* = 7.4, 1.0 Hz, 1H), 4.76 (dd, *J* = 16.3, 4.5 Hz, 1H), 3.64 (ddd, *J* = 12.2, 5.1, 2.3 Hz, 1H), 3.45 (td, *J* =12.2, 3.2 Hz, 1H), 3.16 (ddd, *J* = 15.8, 5.1, 0.9 Hz, 1H), 2.87-2.85 (m, 1H), 2.84-2.81 (m, 1H), 2.53 (t, *J* = 16.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 154.2, 135.0, 133.5, 129.5, 127.3, 127.2, 125.7, 98.7, 56.7, 49.8, 44.1, 30.4; IR (thin film) 1630 (s), 1586, 1581 cm^{-1}; LRMS (TOF ES+), 222.2 (100%) $[M+Na]^+$, 200.2 (40%) $[M+H]^+$; HRMS (TOF ES+), calculated for $C_{13}H_{13}NO+H^+$, 200.1075; found 200.1079. All spectroscopic and analytical properties were identical to those reported in the literature.[17]

*1,1'-(7,11b-Dihydro-6H-pyrido[2,1-a]isoquinoline-1,3-diyl)diethanone (**8**)*

Method A. To **5** (0.131 g, 1.0 mmol) and $Fe(OTf)_2$ (0.05 g, 0.1 mmol) in CH_2Cl_2 (1 mL) under argon was added 4-methoxy-3-buten-2-one **7** (0.204 mL, 2 mmol). The reaction mixture was stirred at rt for 24 h. Purification by silica gel chromatography (4:1, EtOAc:CH_2Cl_2, as eluent) afforded **8** as a yellow solid (0.234 g, 88%): m.p. 225-230 °C; R_f. 0.1 (2:1, EtOAc:hexane as eluent); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.58 (br s, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 0.4 Hz, 1H), 6.70 (d, *J* = 0.4 Hz, 1H), 5.91 (br s, 1H), 3.94 (dt, 13.1, 7.7 Hz, 1H), 3.79 (ddd, 13.1, 8.1, 4.3 Hz, 1H), 3.19 (dt, *J* = 16.4, 8.1 Hz, 1H), 3.09 (ddd, *J* = 16.4, 7.7, 4.3 Hz, 1H), 2.52 (br s, 3H), 2.17 (br s, 3H,) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.8, 191.0, 151.0, 138.3, 135.4, 132.6, 128.8, 127.5, 126.7, 124.7, 109.0, 55.0, 51.7, 31.0, 28.4, 25.0, 24.7; IR (neat) 1644 (s), 1591, 1538 cm^{-1}; UV (MeOH nm) 409 (Σ 5841), 315 (Σ 20076), 228 (Σ 11361), 212 (Σ 13139); LRMS (TOF ES+), 290.3 (100%) $[M+Na]^+$, 268.3 $[M+H]^+$; HRMS (TOF ES+), calculated for $C_{17}H_{17}NO_2+H^+$, 268.1338; found 268.1335. *Anal.* calcd: C, 76.38, H, 6.41, N, 5.24, found: C, 75.85, H, 6.38, N, 5.13. *Method B.* Compound **8** was also isolated and purified by trituration as follows: To **5** (0.131 g, 1.0 mmol) and $Sc(OTf)_3$ (0.049 g, 0.1 mmol) in CH_2Cl_2 (1.5 mL) under argon was added 4-methoxy-3-buten-2-one **7** (0.408 mL, 4 mmol). The reaction mixture was stirred at rt for 48 h, filtered and washed with Et_2O, followed by EtOAc drop by drop whilst filtering, in order to give **8** as a yellow solid (0.133 g, 50%). All spectroscopic and analytical properties were identical to those reported in Method A.

*1,3,5-Triacetylbenzene (**9**)*

To 4-methoxy-3-buten-2-one **7** (0.102 mL, 1.0 mmol) in $CHCl_3$ (0.5 mL) was added $Yb(OTf)_3$ (0.124 g, 0.2 mmol) and the reaction mixture was stirred at rt for 7 days. Purification by silica gel chromatography (3:2 diethyl ether:hexane as eluent) afforded **9** as a white solid (0.030 g, 45%): m.p. 158-159 °C (lit. 158-160 °C)[18]; R_f. 0.16 (2:1, diethyl ether:hexane as eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 3 × 1H), 2.71 (br s, 3 × 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 196.7, 138.1, 131.9, 27.0; IR (thin film) 1687 (s), 1361, 1225 cm^{-1}; LRMS (FTMS NES+), 222.1 (100%) $[M+NH_4]^+$, 205.1 (16%), $[M+H^+]$; HRMS (FTMS ES+), calculated for $C_{12}H_{12}O_3+NH_4^+$, 222.1125; found 222.1127; *Anal.* Calcd: C, 70.57, H, 5.92, found: C, 69.19, H, 5.89. All spectroscopic and analytical properties were identical to those reported in the literature.[18]

*1,1'-(1-Allyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)diethanone (**19**)*

To **16** (0.145 g, 1.0 mmol) and $Sc(OTf)_3$ (0.049 g, 0.1 mmol) in $CHCl_3$ (1.5 mL) under argon was added 4-methoxy-3-buten-2-one **7** (0.408 mL, 4.0 mmol). The reaction mixture was stirred at rt for 2 days, washed with sat. (aq) $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel chromatography (1:9, EtOAc:diethyl ether, as eluent) afforded **19** as a yellow oil (0.089 g, 31%): m.p. 118-119 °C; R_f. 0.18 (1:9, EtOAc:diethyl ether, as eluent); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.14-7.11 (m, 1H), 7.13 (s, 2H), 5.94 (ddt, *J* = 17.0, 10.5, 5.6 Hz, 1H), 5.38 (dtd, *J* = 10.5, 1.6, 0.9 Hz, 1H), 5.36 (dtd, *J* = 17.0, 1.6, 0.9 Hz, 1H), 5.18 (s, 1H), 4.10 (dt, *J* = 5.6, 1.6 Hz, 2H), 2.15 (br s, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.2, 145.9, 138.0, 132.5, 128.3, 128.3, 126.6, 119.6, 119.5, 57.3, 35.9, 25.7; IR (thin film) 1633 (C=O), 1566 cm^{-1}; LRMS (TOF ES+), 304.3 (100%) $[M+Na]^+$, 282.3 (35%) $[M+H]^+$, 176.2 (20%), 146.2 (20%); HRMS (TOF ES+), calculated for $C_{18}H_{19}NO_2+H^+$, 282.1494; found 282.1495; *Anal.* Calcd: C, 76.84, H, 6.81, N, 4.98, found: C, 76.65, H, 6.84, N, 4.94. All spectroscopic and analytical data were identical to those reported in the literature.[14]

*1,1'-(1-Allyl-4-(dimethoxymethyl)-1,4-dihydropyridine-3,5-diyl)diethanone (**20**)*

To **17** (0.143 g, 1.0 mmol) and $Sc(OTf)_3$ (0.049 g, 0.1 mmol) in $CHCl_3$ (1.5 mL) under argon was added 4-methoxy-3-buten-2-one **7** (0.408 mL, 4.0 mmol). The reaction mixture was stirred at rt for 2 days, washed with sat. (aq) $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel chromatography (1:9, EtOAc:diethyl ether, to EtOAc, as eluent) afforded **20** as a dark orange oil (0.045 g, 20%): R_f. 0.15 (EtOAc, as eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 5.86 (ddt, *J* = 16.7, 10.2, 5.0 Hz, 1H), 5.33 (dtd, *J* = 16.7, 1.6, 0.9 Hz, 1H), 5.29 (dtd, *J* = 10.2, 1.6, 0.9 Hz, 1H), 4.45 (d, *J* = 4.0 Hz, 1H), 4.03 (dt, *J* = 5.0, 1.6 Hz, 2H), 3.97 (d, *J* = 4.0 Hz, 1H), 3.22 (br s, 6H), 2.26 (br s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 139.9, 132.7, 118.8, 114.9, 107.3, 57.3, 55.9, 33.3, 25.5; IR (thin film) 1639 (C=O), 1567 cm^{-1}; LRMS (TOF ES+), 302.3 (100%) $[M+Na]^+$, 280.3 (60%) $[M+H]^+$, 176.2 (20%), 248.2 (30%); HRMS (TOF ES+), calculated for $C_{15}H_{21}NO_4+Na^+$, 302.1368; found 302.1382. All spectroscopic and analytical data were identical to those reported in the literature.[14]

*p-Methoxyphenylamino-4-butene-3-one-2 (**21**)*

To **16** (0.211 g, 1.0 mmol) in $CHCl_3$ (1 mL) was added 4-methoxy-3-buten-2-one (0.255 mL, 2.5 mmol) and $Sc(OTf)_3$ (0.049 g, 0.1 mmol). The reaction mixture was flushed with argon and stirred at rt for 2 days. The crude was concentrated *in vacuo* and purified by silica gel chromatography (1:9,

EtOAc:diethyl ether, to EtOAc, as eluent) to afford **21** as an orange oil (0.048 g, 25%): R_f. 0.53 (EtOAc, as eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (br d, *J* = 12.0 Hz, 1H), 7.15 (dd, *J* = 12.0, 7.6 Hz, 1H), 7.01-6.97 (m, 2H), 6.90-6.86 (m, 2H), 5.26, (d, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 2.15 (s, 3H) ppm (addition of D_2O caused the signal at δ 11.63 to disappear, and the signal at δ 7.15 to change to a d, *J* = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 156.3, 144.2, 134.2, 117.8, 115.1, 96.7, 55.7, 29.5; IR (thin film) 1636 (C=O), 1597, 1569, 1513, 1479 cm^{-1}; LRMS (TOF ES-), 190.2 (100%) $[M–H]^-$, 175.1 (25%); HRMS (TOF ES-), calculated for $C_{11}H_{13}NO_2–H^+$, 190.0868; found 190.0871. All spectroscopic and analytical properties were identical to those reported in the literature.[16]

*2-(3-Oxobutyl)-3,4-dihydroisoquinolin-2-ium trifluoromethanesulfonate (**23**)*

To **5** (0.131 g, 1.0 mmol) and $Yb(OTf)_3$ (0.124 g, 0.20 mmol) in CH_2Cl_2 (1.5 mL) under argon was added methyl vinyl ketone **22** (0.162 mL, 2 mmol). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. Purification by silica gel chromatography (1:1, EtOAc:hexane, to 100%, EtOAc, as eluent) afforded **24** as a white solid (0.051 g, 25%) and **23** as a yellow oil (0.128 g, 37%): *Rf*. 0.23 (1:1, EtOAc:methanol, as eluent); ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 7.87 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.72 (td, *J* = 7.6, 1.1 Hz, 1H), 7.47 (td, *J* = 7.6, 1.1 Hz, 1H,), 7.35 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.32 (t, *J* = 6.0 Hz, 2H), 4.14 (t, *J* = 8.1 Hz, 2H), 3.29 (t, *J* = 6.0 Hz, 2H), 3.27 (t, *J* = 8.1 Hz, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 206.2, 168.1, 138.6, 136.4, 134.7, 128.7 (q, *J* = 285 Hz), 124.7, 121.9, 119.4, 116.8, 55.6, 49.2, 40.1, 30.1, 25.5; IR ν_{max} (thin film) 1714 (C=O), 1661 (C=N) cm^{-1}; LRMS (TOF ES+), 203.5 (100%) $[M+H]^+$, 201.7 (70%), 132.1 (25%); LRMS (TOF ES-), 149.0 (100%) [OTf]; HRMS (FTMS ES+) calculated for $C_{13}H_{15}NO+H^+$, 202.12264; found 202.12262; HRMS (FTMS ES-), calculated for $CF_3O_3S^–$, 148.95257; found 148.95217.

*2-(3-Oxobutyl)-3,4-dihydroisoquinolin-2-ium iodide (**34**)*

To **5** (0.178 g, 1.35 mmol) and InI_3 (0.234 g, 0.47 mmol) in CH_2Cl_2 (4 mL) under argon was added methyl vinyl ketone **22** (0.125 mL, 1.5 mmol). The reaction mixture was stirred for 4 h and concentrated *in vacuo*. Purification by silica gel chromatography (1:1, EtOAc:hexane, to 100%, EtOAc, as eluent) gave **34** as a pure yellow oil (62 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.04 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H,), 7.35 (d, *J* = 7.6 Hz, 1H), 4.43 (t, *J* = 5.8 Hz, 2H), 4.22 (t, *J* = 8.0 Hz, 2H), 3.50 (t, *J* = 5.7 Hz, 2H), 3.33 (t, *J* = 7.9 Hz, 2H), 2.27 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 205.9, 166.9, 138.2, 136.2, 134.7, 128.7, 128.3, 124.5, 55.7, 50.2, 41.0, 30.7, 25.6; IR ν_{max} (thin film) 3001, 2943, 1706 (C=O), 1660 (C=N), 1575, 1358, 1172 cm^{-1}; LRMS (TOF ES+), 202.6 (100%) $[M+H]^+$. HRMS (FTMS ES+) calculated for $C_{13}H_{15}NO+H^+$, 202.1232; found 202.1218.

*3,4,6,7-Tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**24**)*

Method A. To **5** (0.131 g, 1.0 mmol) and $Yb(OTf)_3$ (0.124 g, 0.20 mmol) in CH_2Cl_2 (1.5 mL) under argon was added methyl vinyl ketone **22** (0.162 mL, 2 mmol). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. Purification by silica gel chromatography (1:1, EtOAc:hexane, to 100% EtOAc, as eluent) afforded **23** as a yellow oil (0.128 g, 37%) and **24** as a white solid (0.051 g, 25%). *Method B.* Compound **5** (0.39 g, 3 mmol) and methyl vinyl ketone **22** (275 µL, 3.3 mmol) were added to a stirring solution of *t*BME (12 mL) under argon. Chloroacetic acid (56.7 mg, 0.6 mmol) was added to the solution and the mixture was stirred overnight (16 h). The resulting solution was partitioned between EtOAc and washed with K_2CO_3 (1 × 20 mL), brine (2 × 20 mL), after which the organic layer was dried over $MgSO_4$. After filtration, the organic layer was concentrated to yield a dark orange oil. Purification by silica gel chromatography (1:1, EtOAc:hexane, to 100% EtOAc, as eluent) afforded **22** as a white solid (0.501 g, 83%): m.p. 75-77 °C (lit. 76-77 °C)[19]; *Rf*. 0.18 (EtOAc, as eluent); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20-7.13 (m, 3H), 7.10-7.06 (m, 1H), 3.59 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.28 (ddd, *J* = 10.8, 5.2, 3.0 Hz, 1H), 3.22-3.12 (m, 2H), 2.96 (ddd, *J* = 14.6, 3.4, 2.4 Hz, 1H), 2.84-2.80 (m, 1H), 2.75-2.67 (m, 2H), 2.63 (td, *J* = 10.6, 3.9 Hz, 1H), 2.50 (ddd, *J* = 14.6, 12.0, 0.9 Hz, 1H), 2.43 (ddd, *J* = 12.0, 3.4, 1.6 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 136.8, 134.1, 129.1, 126.7, 126.3, 124.9, 61.9, 54.9, 50.8, 47.4, 41.2, 29.9; IR ν_{max} (thin film) 1714 (C=O), 1360 cm^{-1}; LRMS (TOF ES+), 202.2 (100%) $[M+H]^+$; HRMS (FTMS ES+), calculated for $C_{13}H_{15}NO+H^+$, 202.12264; found 202.12264. The e.e. was determined by chiral HPLC using OJ-H-CHIRALCEL® column (250 × 4.6 mm), 35 °C, 1 mL/min, 215 nm, hexane:IPA (9:1), *t*R1 = 10.4 min; *t*R2 = 16.7 min. All spectroscopic and analytical properties were identical to those reported in the literature.[28]

Acknowledgments

We thank Merck & Co. supporting this work, the EPSRC for a DTA studentship (to PRG), and the EPSRC National Mass Spectrometry Service, Swansea.

References and notes

1. P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.*, **1998**, 633-640.
2. N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry*, **2000**, *11*, 1645-1680.
3. a) X. G. Huang, A. Q. Zhang, D. L. Chen, Z. H. Jia, X. S. Li, Bioorg. *Med. Chem. Lett.*, **2010**, *20*, 2859-2863; b) B. E. Maryanoff, D. F. McComsey, R. J. Taylor, J. F. Gardocki, *J. Med. Chem*., **1981**, *24*, 79-88.
4. a) V. Jurčík, K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Adv. Synth. Catal.*, **2008**, *350*, 647-651; b) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.*, **2005**, *44*, 4877-4880; c) S. L. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem.-Eur. J.*, **2000**, *6*, 2435-2448; d) K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.*, **1994**, *116*, 10520-10524; e) K. Hattori, H. Yamamoto, *J. Org. Chem.*, **1992**, 57, 3264-3265.
5. S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc*., **1974**, *96*, 7807-7808.
6. a) P. R. Girling, T. Kiyoi, A. Whiting, *Org. Biomol. Chem.*, **2011**, *9*, 3105-3121; b) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron*, **2001**, *57*, 6099-6138; c) G. R. Heintzelman, I. R. Meigh, Y. R. Mahajan, S. M. Weinreb, *Org. React.*, **2005**, *65*, 141–599; d) G. B. Rowland, E. B. Rowland, Q. Zhang, J. C. Antilla, *Curr. Org. Chem.*, **2006**, *10*, 981-1005; h) V. V. Kouznetsov, *Tetrahedron*, **2009**, *65*, 2721-2750; i) G. Masson, C. Lalli, M. Benohoud, G. Dagousset *Chem. Soc. Rev.* **2013**, *42*, 902-923.
7. a) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron*, **2003**, *59*, 2953-2989; b) S. K. Sahu, B. K. Dubey, A. C. Tripathi, M. Koshy, S. K. Saraf, *Mini Rev. Med. Chem.*, **2013**, *13*, 565-583.
8. a) L. Di Bari, S. Guillarme, S. Hermitage, D. A. Jay, G. Pescitelli, A. Whiting, *Chirality*, **2005**, *17*, 323-331; b) A. Bundu, S. Guillarme, J. Hannan, H. Wan, A. Whiting, *Tetrahedron Lett.*, **2003**, *44*, 7849-7850; c) A. K. McFarlane, G. Thomas, A. Whiting, *Tetrahedron Lett*., **1993**, *34*, 2379-2382; d) A. K.

McFarlane, G. Thomas, A. Whiting, *J. Chem. Soc., Perkin Trans. I*, **1995**, 2803-2808

9. a) S. Hermitage, J. A. K. Howard, D. Jay, R. G. Pritchard, M. R. Probert, A. Whiting, *Org. Biomol. Chem.*, **2004**, 2451-2460; b) S. Guillarme, S. Hermitage, J. A. K. Howard, D. A. Jay, A. Whiting, D. S. Yufit, *Synlett*, **2004**, 708-710; c) S. Guillarme, A. Whiting, *Synlett*, **2004**, 711-713; d) S. Hermitage, D. Jay, A. Whiting, *Tetrahedron Lett.*, **2002**, *43*, 9633-9636.
10. a) P. G. Zheng, B. P. Lieberman, S. R. Choi, K. Ploessl, H. F. Kung, *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 3435-3438; b) C. Zorn, B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, L. Citti, *J. Org. Chem.*, **1999**, *64*, 7846-7855.
11. M. C. Elliott, E. Williams, *Org. Biomol. Chem.*, **2003**, *1*, 3038-3047.
12. S. I. Murahashi, Y. Mitsue, T. Tsumiyama, Bull. *Chem. Soc. Jpn.*, **1987**, *60*, 3285-3290; b) V. Kumbaraci, D. Ergunes, M. Midilli, S. Begen, N. Talinli, *J. Heterocycl. Chem.*, **2009**, *46*, 226-230.
13. T. Iwado, K. Hasegawa, T. Sato, M. Okada, K. Sue, H. Iwamura, T. Hiaki, *J. Org. Chem.*, **2013**, *78*, 1949−1954.
14. P. R. Girling, A. S. Batsanov, H. C. Shen, A. Whiting, *Chem. Commun.*, **2012**, *48*, 4893-4895.
15. L. Di Bari, S. Guillarme, J. Hanan, A. P. Henderson, J. A. K. Howard, G. Pescitelli, M. R. Probert, P. Salvadori, A. Whiting, *Eur. J. Org. Chem.*, **2007**, 5771-5779.
16. G. Duguay, C. Metayer, H. Quiniou, *Bull. Soc. Chim. Fr.*, **1974**, 2507-2512.
17. a) S. Cicchi, J. Revuelta, A. Zanobini, M. Betti, A. Brandi, *Synlett*, **2003**, 2305-2308; b) J. Revuelta, S. Cicchi, A. Brandi, *J. Org. Chem.*, **2005**, *70*, 5636-5642.
18. S. I. Murahashi, Y. Mitsue, T. Tsumiyama, *Bull. Chem. Soc. Jpn.*, **1987**, 60, 3285-3290; b) V. Kumbaraci, D. Ergunes, M. Midilli, S. Begen, N. Talinli, *J. Heterocycl. Chem.*, **2009**, *46*, 226-230.
19. J. M. Caroon, R. D. Clark, A. F. Kluge, C.-H. Lee, A. M. Strosberg, *J. Med. Chem.*, **1983**, *26*, 1426-1433.
20. For reviews on asymmetric organocatalysis: a) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.*, **2009**, *38*, 2178-2189; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1520-1543.
21. T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.*, **2003**, *5*, 4301-4304.
22. For example: a) S. Bertelsen, M. Marigo, S. Brandes, Peter Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2006**, *128*, 12973-12980; b) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem. Int. Ed.*, **2008**, *47*, 4012-4015.
23. K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6058-6063.
24. a) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.*, **2011**, *40*, 4539-4549; b) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.*, **2006**, *128*, 9626-9627.
25. A. D. J. Calow, J. J. Carbó, J. Cid, E. Fernández, A. Whiting, *J. Org. Chem.*, **2014**, *11*, 5163-5172.
26. D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.*, **2010**, *132*, 7260-7261.
27. F. De Meester, J. M. Frère, J. L. Piette, P. Jacquemin, L. Grooters, G. Llabres, S. Defays, *J. Heterocyclic Chem.*, **1992**, *29*, 535-541.
28. L. Cui, Y. Peng, L. M. Zhang, *J. Am. Chem. Soc.*, **2009**, *131*, 8394-8395.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.